

REMARKS

This responds to the Final Office Action mailed on August 12, 2009.

No claims are amended, no claims are cancelled, and no new claims are added. As a result, claims 1-4 are pending in this application. Claims 9-12 and 16 remain withdrawn.

Applicants will cancel the appropriate withdrawn claims upon receipt of a listing of allowed claims. Applicants reserve the right to file one or more additional applications covering the subject matter of any non-allowed pending, withdrawn, and cancelled claims.

No new matter is added with this amendment and response.

Exhibits

The following Exhibits are presented.

Exhibit I presents the XRD patterns of tiagabine hydrochloride Polymorph IV and tiagabine hydrochloride recrystallized from acetone.

Exhibit II presents the XRD patterns of tiagabine hydrochloride Polymorph IV and tiagabine hydrochloride recrystallized from acetone overlaid.

Exhibit III shows the XRD patterns of Tiagabine Hydrochloride Recrystallized from Ethyl Acetate and Tiagabine Hydrochloride Polymorph IV

Exhibit IV shows the recorded XRD pattern of tiagabine hydrochloride recrystallized from ethyl acetate and the associated peak list.

Summary of Telephone Interview with Examiner

Upon receipt, Applicants' representative had a telephone interview to discuss the Final Office Action sent on August 12, 2009. Examiner Loewe noted that the rejection over Andersen et al. had been reinstated and the rejection over Gronvald had been maintained as Applicants had not shown that the solid form in those references were different from those claimed. Applicants' representative pointed out that the information requested had already been presented. Examiner Loewe requested Applicants point out in this response where in the previous responses and declarations such information was present.

Applicants' representative thanks Examiner Loewe for the courtesy of the interview.

Rejection of claims under 35 U.S.C. § 102

The 35 USC § 102 rejections over Andersen et al. and Gronvald et al. are maintained.

The Office Action alleges that Applicants have not shown that the solid form in the prior art references is different from the one instantly claimed. The Office Action further alleges that the declaration in relation to the reference of Andersen et al., Exhibit V does not contain the comparison of XRD pattern. Although not explicitly alleged, the Office Action appears to have repeated the § 102 rejection over Andersen et al. presented in the Office Action of August 29, 2008 and the § 102 rejection over Gronvald et al. presented in the Office Actions of August 29, 2008 and May 11, 2009.

Applicants traverse this rejection and provide the following arguments to support their belief that tiagabine hydrochloride Polymorph IV is different from the tiagabine hydrochloride described either by Andersen et al. (*J. Med. Chem.* **1993**, *36*, 1716-1725, pg 1717 and 1722 2nd column) or by Gronvald et al. (U.S. 5,010,090).

The § 102 rejection over Andersen et al.

The Office Action of August 29, 2008 rejected claims 1-4 under 35 U.S.C. § 102(b) for anticipation by Andersen et al. (*J. Med. Chem.* **1993**, *36*, 1716-1725, pg. 1717 and 1722, 2nd column). The Office action alleged that Andersen et al. teaches a solid form of tiagabine hydrochloride obtained by recrystallization from acetone. The Office Action admitted that Andersen et al. does not teach the specific polymorph because the X-ray diffraction data is not disclosed. That Office action concluded that in the absence of further evidence, the tiagabine hydrochloride produced by Andersen et al. by recrystallization from acetone would be expected to have the same crystal polymorph as Applicants' tiagabine hydrochloride. The Office Action requested Applicants to provide a showing of how their claimed Polymorph IV is different (or unobvious from) the polymorph disclosed in the Andersen et al. reference.

The present Office action again requests Applicants provide a comparison of their tiagabine hydrochloride Polymorph IV with that of tiagabine hydrochloride acetone solvate. The

Office Action alleges that Exhibit V of the Amendment and Response filed on February 25, 2009 does not contain the requested comparison of XRD patterns.

The prior art of record teaches that acetone is a poor choice as a solvent for recrystallizing tiagabine hydrochloride.

Applicants respectfully disagree with the allegation that they have not shown that the solid form produced in Andersen et al. is different from Applicants' tiagabine hydrochloride Polymorph IV. Applicants believe that the Amendment and Response filed on February 25, 2009 contained all the information necessary for a comparison of tiagabine hydrochloride acetone solvate as described by Anderson et al. with Applicants' tiagabine hydrochloride Polymorph IV. For the sake of completeness, and for the record, previous arguments relating to the rejection over Andersen et al. are repeated.

Applicants direct the Examiner's attention to the analytical data for tiagabine hydrochloride prepared by Andersen et al. by recrystallization from acetone as reported at page 1722, column 2, 2nd line from the bottom. It shows that Andersen discloses that tiagabine hydrochloride prepared from acetone is a solvate having the formula C₂₀H₂₅NO₂S₂:0.75C₃H₆O.

Applicants further direct the Examiner's attention to U.S. Patent 5,354,760 (Petersen et al.) cited on page 1 of the present Application and submitted in the IDS filed August 25, 2006. At column 1, lines 49-52, the '760 patent reads: "Use of alternative organic solvents such as acetonitrile, butyl acetate, toluene, acetone, dichloromethane etc. also gives products containing various amounts of the used crystallizing solvent." Applicants believe that this disclosure in U.S. 5,354,760 provides the showing requested in the Office Action that Applicants' tiagabine hydrochloride Polymorph IV cannot be the same polymorph obtained by Andersen et al. by recrystallization from acetone.

Examiner's attention is again directed to the **Declaration under 37 C.F.R. 1.132** paragraphs 10 and 11, submitted on February 25, 2009 where Dr. K. Srinivasu declares that under his direction, his laboratory recrystallized tiagabine hydrochloride from acetone according to the process disclosed in Exhibit V and found it to be a Tiagabine hydrochloride acetone solvate.

In his declaration, Dr. K Srinivasu declared:

10. In the Office Action mailed August 29, 2008, the Examiner rejected claims 1-4 under 35 U.S.C. § 102(b) or in the alternative, under 35 U.S.C. 103(a) as allegedly being anticipated or obvious over Andersen et al. (*J. Med. Chem.* **1993**, *36*, 1716-1725). Under my direction, our laboratory studied the recrystallization of Tiagabine hydrochloride from acetone by the procedure disclosed in Exhibit V
11. Our study indicated that when Tiagabine hydrochloride was recrystallized from acetone, we obtained the material as solvate of acetone with an acetone content of 42,149 ppm (i.e. tiagabine hydrochloride:acetone in a mole ratio of 1:0.34). The XRD pattern of this material, shown in the attached Exhibit VI as 7022/F/691/32B, is different from that of Tiagabine hydrochloride Polymorph IV. Thus, our observations are in accord with those disclosed in the '951 patent (column 1, lines 45-50).

Thus, Dr. Srinivasu found that tiagabine hydrochloride recrystallized from acetone according to the procedure of Andersen et al. contained approximately 25 mol% acetone. In contrast, Applicants' tiagabine hydrochloride Polymorph IV is essentially solvent free. See specification, page 8, below the table, wherein it states that "Stable polymorphic forms III, IV and amorphous form are substantially free of solvent."

Applicants provide a showing that tiagabine hydrochloride Polymorph IV differs from that of the polymorph disclosed in Andersen et al. (*J. Med. Chem.*).

The XRD pattern and the characteristic peaks and peak intensities (expressed in degrees 2 theta) of tiagabine hydrochloride acetone solvate are presented in Exhibit VI of the response filed February 25, 2009. The XRD pattern is shown at Exhibit VI, page 1. The Examiner is invited to compare the XRD pattern of tiagabine hydrochloride acetone solvate shown at Exhibit VI with that of the XRD pattern of tiagabine hydrochloride Polymorph IV shown in Fig. 2 of the present application (U.S. Serial No. 10/583,805). The previously presented XRD patterns of these two compounds are here again presented, this time one above another in Exhibit I for convenience. The XRD patterns are presented overlaid in Exhibit II. The Examiner is invited to compare the XRD patterns of these two compounds to confirm that the two compounds have different XRD patterns.

In addition, Examiner's attention is directed to the table below, comparing, side-by-side, the XRD characteristic peaks of Applicants' tiagabine hydrochloride Polymorph IV with those of the acetone solvate. This data has also previously been presented. The table of characteristic peaks and peak intensities is shown at Exhibit VI, pages 2-3 of the response filed February 25, 2009. The table of characteristic peaks of tiagabine hydrochloride polymorph IV is presented on page 3 of the specification as filed and also recited in claim 2. The Examiner is requested to compare the characteristic peaks of these two compounds to confirm that the characteristic XRD peaks of the two compounds are different. The differentiating peaks are underlined and **bolded**.

Comparison of Characteristic XRD peaks of Tiagabine Hydrochloride Polymorph IV
with those of Tiagabine Hydrochloride crystallized from Acetone

| Polymorph IV degrees 2 theta | Acetone Crystallized degrees 2 theta |
|---------------------------------|--|
| 4.46 | — |
| 5.03 | — |
| 5.48 | — |
| 6.46 | — |
| 7.46 | — |
| — | 7.89 |
| 8.11 | — |
| 8.35 | — |
| 9.45 | — |
| 10.29 | — |
| — | 11.26 |
| <u>11.41</u> | — |
| 11.94 | — |
| 12.32 | — |
| — | 12.49 |
| 12.91 | 12.89 |
| — | 13.14 |

| | |
|--------------|--------------|
| 13.59 | 13.53 |
| <u>13.83</u> | — |
| — | 14.32 |
| <u>14.52</u> | — |
| 14.85 | 14.89 |
| 15.36 | — |
| — | 15.52 |
| 15.97 | 15.93 |
| 16.26 | 16.17 |
| — | 16.61 |
| <u>16.83</u> | — |
| — | 17.25 |
| — | 17.66 |
| 17.85 | — |
| — | 18.32 |
| 18.36 | — |
| 18.59 | 18.62 |
| <u>18.85</u> | — |
| <u>19.25</u> | — |
| 19.45 | 19.43 |
| — | 19.62 |
| — | 19.86 |
| — | 20.06 |
| 20.36 | 20.30 |
| 20.98 | 20.91 |
| 21.59 | — |
| — | 21.78 |
| — | 21.98 |
| 22.15 | — |
| 22.49 | 22.57 |
| 22.99 | 23.07 |
| — | 23.45 |

AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.116 - EXPEDITED PROCEDURE

Serial Number: 10/583,805

Filing Date: June 22, 2006

Title: NOVEL STABLE POLYMORPHIC FORMS OF AN ANTICONVULSANT

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| | |
|--------------|--------------|
| 23.67 | 23.75 |
| <u>23.96</u> | — |
| 24.75 | 24.80 |
| — | 25.20 |
| 25.33 | — |
| <u>25.62</u> | — |
| 25.97 | 25.92 |
| 26.43 | 26.44 |
| — | 26.67 |
| 27.02 | — |
| — | 27.25 |
| 27.48 | — |
| — | 27.70 |
| 27.94 | — |
| 28.16 | — |
| — | 28.27 |
| — | 28.67 |
| 28.88 | — |
| — | 29.08 |
| 29.63 | 29.60 |
| — | 29.95 |
| 30.27 | — |
| — | 30.42 |
| 30.87 | — |
| — | 31.16 |
| 31.54 | — |
| — | 31.86 |
| 32.11 | 32.12 |
| 32.52 | 32.52 |
| 32.96 | — |
| — | — |
| 33.52 | 33.52 |

| | |
|-------|--------------|
| — | — |
| 33.89 | — |
| 34.45 | — |
| — | 35.03 |
| 35.33 | 35.35 |
| 35.59 | — |
| 36.02 | — |
| 36.53 | 36.52 |
| 36.77 | 36.66 |
| 37.28 | — |
| 37.75 | — |
| 38.24 | — |
| — | 38.42 |
| 39.12 | — |
| — | 39.35 |

In view of the above remarks, Applicants believe that the anticipation rejection of claims 1-4 under 35 U.S.C. §102 over Andersen et al. has been fully addressed. Reconsideration withdrawal of the rejection of claims 1-4 over Andersen et al. is respectfully requested.

The § 102 rejection over Gronvald et al.

The Office Action of August 29, 2008 rejected claims 1-4 under 35 U.S.C. § 102(b) for anticipation by Gronvald et al. (U.S. Patent No. 5,010,090). The Office Action asserted that the '090 patent teaches a solid form of tiagabine hydrochloride obtained by recrystallization from ethyl acetate. The Office Action admitted that the '090 patent does not teach the specific polymorph because the X-ray diffraction data is not disclosed. The Office action concluded that in the absence of further evidence, the tiagabine hydrochloride produced as disclosed in the '090 patent by recrystallization from ethyl acetate would be expected to have the same crystal polymorph as Applicants' tiagabine hydrochloride. The Office Action requested Applicants provide a showing of how their claimed Polymorph IV is different from the polymorph disclosed in the '090 patent. The Final Office Action of May 11, 2009 repeated the rejection, again

alleging that Applicants have not shown that the solid form produced in Gronvald et al. is different from Applicant's tiagabine hydrochloride Polymorph IV.

The present Final Office action again requests Applicants provide a comparison of their tiagabine hydrochloride Polymorph IV with that of tiagabine hydrochloride recrystallized from ethyl acetate.

Applicants respectfully disagree with the allegation that they have not shown that the solid form produced in Gronvald et al. is different from Applicants' tiagabine hydrochloride Polymorph IV. Applicants believe that the Amendment and Response filed on February 25, 2009 and that filed July 8, 2009 each contained all the information necessary for a comparison of tiagabine hydrochloride acetone solvate as described by Gronvald et al. with Applicants' tiagabine hydrochloride Polymorph IV. For the sake of completeness, and for the record, previous arguments relating to the rejection over Andersen et al. are repeated.

Applicants provide a showing that tiagabine hydrochloride Polymorph IV differs from that of the polymorph disclosed in Gronvald et al. (the '090 patent).

The Office Action requests that Applicants provide a showing of how their claimed Polymorph IV differs from that of the polymorph disclosed in Gronvald et al. (the '090 patent).

Examiner's attention is directed to the **Declaration under 37 C.F.R. 1.132** paragraphs 7 and 8, submitted on July 8, 2009, where Dr. K. Srinivasu declares that under his direction, his laboratory attempted to recrystallize tiagabine hydrochloride from ethyl acetate and found that it required an inordinately large amount of solvent, and gave tiagabine hydrochloride that was brown in color and had a blue tinge. The color of this product was different from that of samples of tiagabine hydrochloride Polymorph IV prepared as described in the Applicants' patent application. The experimental conditions for the recrystallization of tiagabine hydrochloride from ethyl acetate are provided in **Exhibit I** of the response filed on July 8, 2009.

Examiner's attention is further directed to the **Declaration under 37 C.F.R. 1.132** paragraph 9, and **Exhibit II**, both submitted on July 8, 2009, where Dr. K. Srinivasu declares that a sample of the tiagabine hydrochloride, prepared by recrystallization from ethyl acetate, was submitted to Professor T. N. Guru Row for XRD analysis. Professor Guru Row attempted to obtain XRD data for the sample so that it could be compared with Applicants' sample of

tiagabine hydrochloride Polymorph IV as disclosed and claimed in the present patent application, U.S. Serial No. 10/583,805. As can be seen from Professor Guru Row's letter, "Attempts to obtain a unique indexing on the pattern failed as we perceive that there is more than one phase associated with the sample or the sample is contaminated with impurity peaks." Professor Row's letter clearly indicates that the tiagabine hydrochloride, obtained by recrystallization from ethyl acetate, is contaminated with impurity peaks.

Examiner's attention is further directed to the **Declaration under 37 C.F.R. 1.132** paragraph 9, and **Exhibit III**, both submitted on July 8, 2009, where Dr. K. Srinivasu declares that Professor Guru Row compared the recorded XRD pattern of tiagabine hydrochloride, (Batch No. 7022/F/691/32A2) recrystallized from ethyl acetate, with that of the simulated pattern of tiagabine hydrochloride Polymorph IV, prepared as described in the present patent application.

Exhibit III of the Amendment and Response submitted on July 8, 2009 compares the recorded XRD pattern of tiagabine hydrochloride Polymorph IV with that of tiagabine hydrochloride recrystallized from ethyl acetate. The XRD patterns are presented one above another on the first page of Exhibit III. The top pattern is that of tiagabine hydrochloride recrystallized from ethyl acetate. The bottom pattern is that of tiagabine hydrochloride Polymorph IV, (generated from the stored characteristic peak and intensity data). The two compounds have different XRD patterns. The XRD patterns are presented in overlay on the second page of Exhibit III. Here again, the differences in the XRD pattern between the two materials are apparent. The XRD patterns are included in this response as Exhibit III for convenience.

Applicants would first like to explain the term "simulated pattern of tiagabine hydrochloride Polymorph IV" used in Professor Guru Row's letter. The XRD data for tiagabine hydrochloride Polymorph IV had already been recorded. This was done when preparing the present patent application. The XRD pattern is shown in Fig. 2 of the present patent application. The characteristic peaks and intensities (expressed in degrees 2 theta) were already stored in Professor Guru Row's computers. Therefore, the XRD pattern for tiagabine hydrochloride Polymorph IV shown in Exhibit III of Professor Guru Row's declaration submitted on July 8, 2009 was generated using the previously stored data. This allowed it to be superimposed on the XRD pattern determined for tiagabine hydrochloride recrystallized from ethyl acetate.

Thus, the data described in Professor Row's letter clearly indicates that the tiagabine hydrochloride, obtained by recrystallization from ethyl acetate, is not the same as the new and previously unknown tiagabine hydrochloride Polymorph IV as presently claimed by Applicants.

In addition, Examiner's attention is directed to the table below comparing, side-by-side, the XRD characteristic peaks of Applicants' tiagabine hydrochloride Polymorph IV with those of the tiagabine hydrochloride recrystallized from ethyl acetate. The Examiner is requested to compare the characteristic peaks of these two compounds to confirm that the characteristic XRD peaks of the two compounds are different. The XRD pattern and associated characteristic peaks are also shown in Exhibit IV. The differentiating peaks are underlined and **bolded**.

Comparison of Characteristic XRD peaks of Tiagabine Hydrochloride Polymorph IV
with those of Tiagabine Hydrochloride crystallized from Ethyl acetate

| Polymorph IV degrees 2 theta | Ethyl acetate Crystallized degrees 2 theta |
|---------------------------------|--|
| 4.46 | — |
| 5.03 | — |
| — | 5.15 |
| 5.48 | — |
| 6.46 | — |
| — | 6.53 |
| 7.46 | — |
| 8.11 | — |
| 8.35 | — |
| 9.45 | — |
| — | 9.28 |
| 10.29 | — |
| 11.41 | 11.46 |
| 11.94 | — |
| 12.32 | 12.39 |
| 12.91 | 12.95 |

| | |
|--------------|--------------|
| <u>13.59</u> | — |
| 13.83 | — |
| — | 13.74 |
| 14.52 | 14.60 |
| 14.82 | — |
| 14.85 | 14.87 |
| — | 15.08 |
| 15.36 | 15.39 |
| 15.97 | 16.02 |
| 16.26 | 16.33 |
| 16.83 | 16.74 |
| — | 16.97 |
| 17.85 | — |
| — | 17.68 |
| 18.36 | — |
| 18.59 | 18.49 |
| 18.85 | 18.81 |
| <u>19.25</u> | — |
| 19.45 | 19.43 |
| 20.36 | 20.47 |
| 20.98 | 21.00 |
| 21.59 | — |
| 22.15 | — |
| — | 22.32 |
| — | 22.66 |
| <u>22.49</u> | — |
| 22.99 | 23.11 |
| 23.67 | 23.77 |
| 23.96 | 23.95 |
| 24.75 | 24.83 |
| 25.33 | 25.25 |

AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.116 - EXPEDITED PROCEDURE

Serial Number: 10/583,805

Filing Date: June 22, 2006

Title: NOVEL STABLE POLYMORPHIC FORMS OF AN ANTICONVULSANT

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| | |
|--------------|--------------|
| <u>25.62</u> | — |
| <u>25.97</u> | — |
| 26.43 | 26.41 |
| — | 26.74 |
| 27.02 | 27.22 |
| 27.48 | — |
| 27.94 | 27.99 |
| 28.16 | — |
| 28.88 | 28.88 |
| — | — |
| 29.63 | — |
| — | — |
| 30.27 | 30.39 |
| 30.87 | — |
| — | — |
| 31.54 | 31.59 |
| 32.11 | — |
| 32.52 | — |
| 32.96 | — |
| — | 32.79 |
| 33.52 | — |
| — | 33.70 |
| 33.89 | — |
| 34.45 | — |
| — | 35.15 |
| 35.33 | — |
| 35.59 | 35.68 |
| 36.02 | — |
| 36.53 | — |
| 36.77 | 36.88 |
| 37.28 | 37.39 |

| | |
|--------|-------|
| 37.75 | — |
| 38.24 | — |
| 39.12. | 39.32 |
| — | 42.07 |
| <hr/> | |

The prior art of record also teaches that ethyl acetate is a poor choice as a solvent for recrystallizing tiagabine hydrochloride.

Applicants also direct the Examiner's attention to U.S. Patent 5,958,951 (Arndt et al.) cited on page 1 of the present Application (U.S. Serial No 10/583,805) and submitted in the IDS filed August 25, 2006. At column 1, line 39-49, the '951 patent states "The alternative product, which is disclosed in the U.S. Pat. No. 5,010,090 (column 8, line 62) [Gronvald et al.] can only be prepared through a labor-intensive process as described, using ethyl acetate. Furthermore, analysis has shown that products manufactured by this process contain unwanted amounts of the crystallizing solvent. Other organic solvents may be used in the isolation of the product, but organic solvents will often form chlathrates, i.e. solvates of tiagabine hydrochloride and the resp. organic solvent." Applicants believe that this disclosure in U.S. 5,958,951 provides further showing that Applicants' tiagabine hydrochloride Polymorph IV cannot be the same polymorph obtained by Gronvald et al. by recrystallization from ethyl acetate – if in fact it was actually recrystallized from ethyl acetate as noted below.

Applicants further direct the Examiner's attention to U.S. Patent 5,354,760 (Petersen et al.) cited on page 1 of the present Application and submitted in the IDS filed August 25, 2006. At column 1, lines 33-51 the '760 patent discloses that tiagabine hydrochloride can be recrystallized from ethyl acetate (citing the Danish equivalent of Gronvald et al. above). At column 1, lines 46-48, the '760 patent states "Furthermore analysis has shown that products manufactured by this process contain unwanted amounts of the crystallizing solvent ethyl acetate." Additionally, at column 1, lines 49-52, the '760 patent continues, "Use of alternative organic solvents such as acetonitrile, butyl acetate, toluene, acetone, dichloromethane etc. also gives products containing various amounts of the used crystallizing solvent." Applicants believe that these disclosures in U.S. 5,354,760 provide additional showings, as requested in the Office

Action, that Applicants' tiagabine hydrochloride Polymorph IV cannot be the same polymorph obtained by Gronvald et al. by recrystallization from ethyl acetate.

Gronvald et al. is not enabling. The reference does not describe the recrystallization of tiagabine hydrochloride from ethyl acetate.

A careful reading of the footnotes to Table I, in columns 9 and 10 of Gronvald et al. indicates that compounds labeled with a "*" were crystallized from ethyl acetate, isopropanol, acetone, or water. Gronvald et al. is silent as to which solvents were used successfully to recrystallize which compounds. The disclosure in Gronvald et al. about recrystallization of tiagabine from ethyl acetate is limited to the description in the footnotes.

Furthermore, when Applicants attempted to recrystallize tiagabine hydrochloride from ethyl acetate, they obtained an impure product. See Points Number 7 and 8 of the enclosed **Rule 132 Declaration** of Dr. K. Srinivasu.

Additional remarks.

Furthermore, both Arndt et al. and Petersen et al. teach that recrystallization of tiagabine hydrochloride from ethyl acetate results in a product containing a large amount of solvent. A large amount of solvent would be expected to result in any crystals formed having different unit cell parameters and XRD peaks than those recited in Applicants' claims.

In view of the above remarks, Applicants believe that the anticipation rejection of claims 1-4 under 35 U.S.C. §102 over Gronvald et al. has been fully addressed. Reconsideration withdrawal of the rejection of claims 1-4 over Gronvald et al. is respectfully requested.

AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.116 - EXPEDITED PROCEDURE

Serial Number: 10/583,805

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CONCLUSION

Applicant respectfully submits that pending claims 1-4 are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6961 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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Date September 24, 2009

By *Louis M. Leichter*
Louis M. Leichter, Ph.D., J.D.
Reg. No. 34,657

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 24 day of September, 2009.

John D. Gustav-Wrathall

Name

John D. Gustav-Wrathall
Signature

Exhibit I - XRD patterns of Tiagabine Hydrochloride Polymorph IV (Top) and
Tiagabine Hydrochloride Recrystallized from Acetone (Bottom)

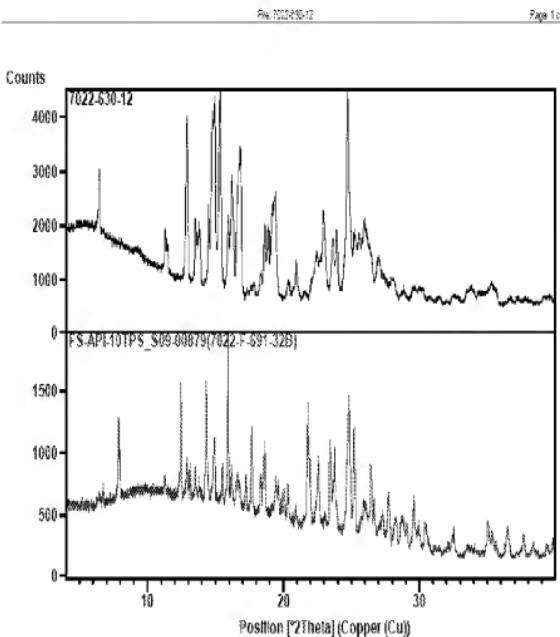


Exhibit II – XRD patterns of Tiagabine Hydrochloride Polymorph IV and
Tiagabine Hydrochloride Recrystallized from Acetone Overlaid

File: 7022-530-12

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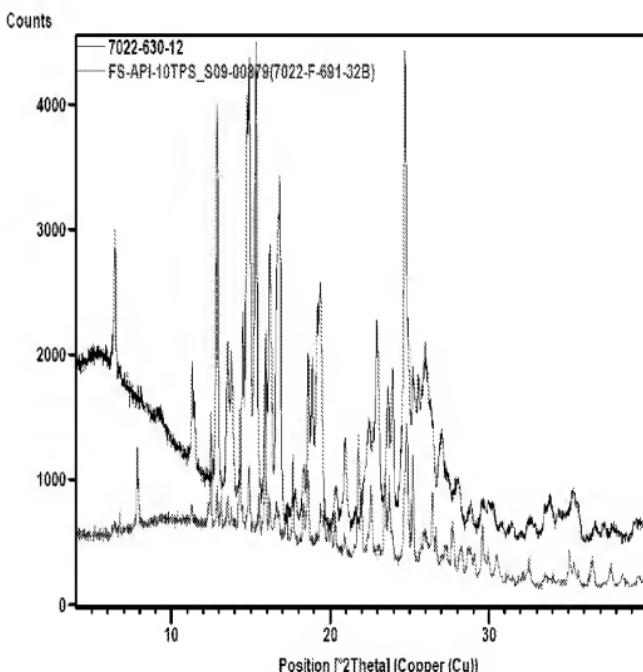
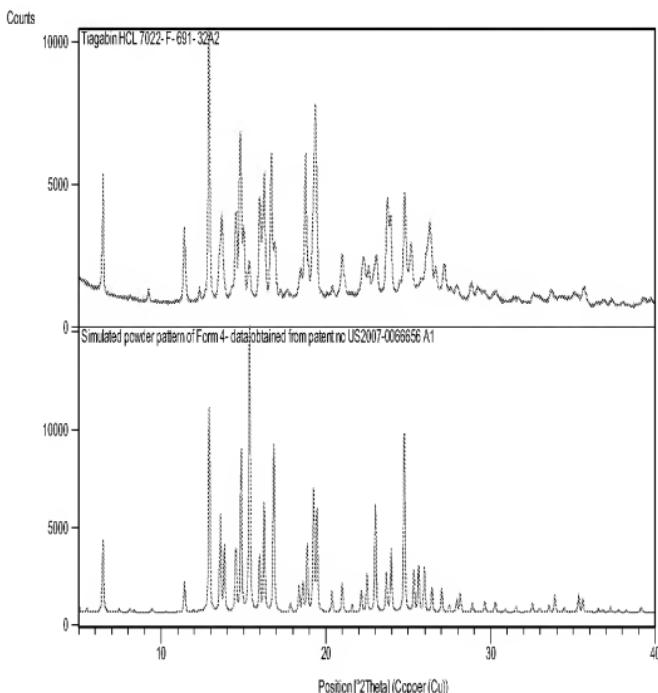


Exhibit III - XRD patterns of Tiagabine Hydrochloride Recrystallized from Ethyl Acetate (Top) and Tiagabine Hydrochloride Polymorph IV (Bottom)



AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.116 - EXPEDITED PROCEDURE

Serial Number: 10583,805

Filing Date: June 22, 2006

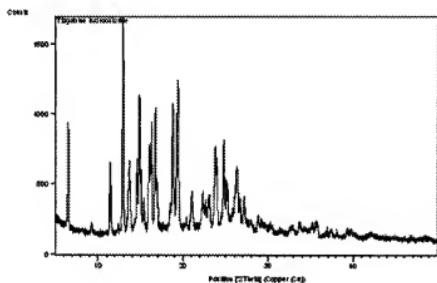
Title: NOVEL STABLE POLYMORPHIC FORMS OF AN ANTICONVULSANT

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Dkt: 2867.002US1**Exhibit IV - The recorded XRD pattern of tiagabine hydrochloride recrystallized from ethyl acetate and the associated peak list.**

Date: 18/03/2009 Time: 9:55:05 AM File: Tiagabine hydrochloride User: Sun

Anchor Scan Parameters

Dataset Name: Tiagabine hydrochloride
File Name: C:\XRD\2JUN\4-MARCH 2009\RaJ\8\Tiagabine hydrochloride.xrdml
Measurement Date / Time: 18/03/2009 4:36:10 PM
Operator: Administrator
Start Position [2θ]: 5.0012
End Position [2θ]: 49.9932
Step Size [2θ]: 0.0003
Scan Step Time [s]: 162.9492
Divergence Slit Type: Fixed
Divergence Slit Size [mm]: 0.2393
Anode Material: Cu
K-A1/k1 [Å]: 1.54060
K-A1/k2 [Å]: 1.54453
K-A2 [Å]: 1.53255
K-A2 / K-A1 Ratio: 0.50000
Generator Settings: 30 mA, 40 kV

Graphics**Peak List**

| Pos. [°2θ] | Height[cts] | Area[cts] | FWHM[°2θ] | d-spacing[Å] | Rel. Int. [%] |
|------------|-------------|-----------|-----------|--------------|---------------|
| 5.0012 | 33.93 | 14.43 | 0.0787 | 13.54614 | 46.81 |
| 6.5252 | 729.81 | 56.67 | 0.0787 | 13.54614 | 4.65 |
| 9.2831 | 72.46 | 9.00 | 0.1260 | 9.52691 | 33.25 |
| 11.4551 | 518.45 | 48.31 | 0.0945 | 7.72496 | 4.08 |
| 12.3866 | 63.55 | 7.90 | 0.1260 | 7.14605 | 100.00 |
| 12.4550 | 150.88 | 19.72 | 0.1102 | 6.94621 | 32.51 |
| 13.7374 | 506.88 | 55.11 | 0.1102 | 6.94626 | 30.94 |
| 14.5956 | 482.35 | 52.44 | 0.1102 | 6.06909 | 61.73 |
| 14.8656 | 962.43 | 134.52 | 0.1417 | 5.95948 | 27.01 |
| 15.0780 | 421.15 | 26.16 | 0.0630 | 5.87601 | 14.38 |
| 15.1097 | 229.48 | 20.49 | 0.0945 | 5.77006 | 30.78 |
| 16.0193 | 599.84 | 55.90 | 0.0945 | 5.42764 | 21.29 |
| 16.3317 | 719.00 | 67.00 | 0.0945 | 5.42764 | 46.12 |
| 16.7447 | 862.11 | 93.72 | 0.1102 | 5.29469 | 55.30 |
| 16.9650 | 331.97 | 25.78 | 0.0787 | 5.22644 | 21.29 |
| 17.6785 | 48.70 | 4.54 | 0.0945 | 5.01708 | 3.12 |
| 18.4904 | 139.64 | 19.52 | 0.1417 | 4.79858 | 8.96 |

AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.116 - EXPEDITED PROCEDURE

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Serial Number: 10/583,805

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Filing Date: June 22, 2006

Title: NOVEL STABLE POLYMORPHIC FORMS OF AN ANTICONVULSANT

| Date: 18/03/2009 | Time: 9:55:05 AM | File: Tiagabine hydrochloride | User | Sum |
|------------------|------------------|-------------------------------|--------|---------|
| 19.8064 | 858.96 | 106.72 | 0.1260 | 4.71864 |
| 19.4253 | 1022.62 | 190.58 | 0.1889 | 4.56968 |
| 20.4696 | 70.84 | 8.80 | 0.1260 | 4.33885 |
| 20.9993 | 224.68 | 31.41 | 0.1417 | 4.23058 |
| 22.3207 | 239.97 | 44.72 | 0.1889 | 3.98302 |
| 22.6609 | 185.35 | 17.37 | 0.1889 | 3.92410 |
| 23.2206 | 220.05 | 43.62 | 0.1889 | 3.84897 |
| 23.7733 | 516.12 | 53.69 | 0.0945 | 3.74316 |
| 23.9505 | 477.30 | 59.30 | 0.1260 | 3.71556 |
| 24.8331 | 623.62 | 87.17 | 0.1417 | 3.58546 |
| 25.2541 | 301.78 | 42.18 | 0.1417 | 3.52664 |
| 26.4093 | 407.48 | 88.60 | 0.2204 | 3.37498 |
| 26.5819 | 196.66 | 24.19 | 0.1889 | 3.33045 |
| 27.2202 | 204.63 | 34.49 | 0.1574 | 3.27622 |
| 27.9889 | 80.09 | 14.93 | 0.1889 | 3.18796 |
| 28.8832 | 114.79 | 21.39 | 0.1889 | 3.09125 |
| 30.3943 | 63.82 | 19.82 | 0.3149 | 2.94092 |
| 31.5866 | 36.76 | 13.70 | 0.3779 | 2.83258 |
| 32.7869 | 58.14 | 28.90 | 0.5038 | 2.73158 |
| 33.1049 | 30.55 | 14.96 | 0.4534 | 2.65924 |
| 35.1531 | 81.42 | 20.23 | 0.2519 | 2.53244 |
| 35.6767 | 103.89 | 19.36 | 0.1889 | 2.51666 |
| 36.8751 | 37.94 | 7.07 | 0.1889 | 2.43759 |
| 37.3906 | 52.13 | 9.72 | 0.1889 | 2.40515 |
| 39.3202 | 51.56 | 9.61 | 0.1889 | 2.29146 |
| 42.0682 | 43.64 | 35.75 | 0.6144 | 2.14613 |
| | | | | 2.80 |